## REMARKS

In response to the Office Action dated July 29, 2004, Applicants have cancelled Claim 15 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended Claims 1-12, and 14. Applicants maintain that the amendments add no new matter and are fully supported by the specification as originally filed. For example, support for the amendments to Claims 1-5 can be found in Example 18 beginning at paragraph [0529], as well as paragraph [0336] of the specification. Support for the amendment to Claim 14 can be found in the definition of stringent conditions in paragraph [0227] of the specification.

Claims 1-14, and 16-20 are presented for examination. Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed July 29, 2004. For the reasons set forth below, Applicants respectfully traverse.

The changes made to the Specification and Claims by the current amendment, including ~~deletions~~ and additions, are shown herein with deletions designated with a strikethrough and additions underlined.

**Specification**

The disclosure was objected to by the Examiner as containing browser-executable code. The specification has been amended to delete these hyperlinks.

**Correction of Inventorship under 37 CFR §1.48(b)**

Applicant requests that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

**Priority**

The PTO has stated that because applications 60/100,930 [sic], PCT/US99/20111 and 09/403,297 do not list or refer to SEQ ID NO: 93 or Figure 93, and because the present application lacks utility, the priority under 35 U.S.C. § 120 is set at the instant filing date, May 8, 2002. Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 5, 2002. The preliminary amendment states that the instant application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US

Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, with is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to, US Application 09/403297 filed 10/18/1999, now abandoned, which is the National Stage filed under 35 U.S.C. § 371 of PCT Application PCT/US99/20111 filed 9/1/1999, which claims priority under 35 U.S.C. § 119 to US Provisional Application 60/100683 filed 9/17/1998.

The sequences of SEQ ID NO:93 and 94 were first disclosed in US Provisional Application 60/100683 filed 9/17/1998 as SEQ ID NO: 1 and 2 and in Figures 1 and 2. These same sequences were disclosed in PCT/US99/20111 and in 09/403,297 as SEQ ID NO: 224 and 225, Figures 127 and 128. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed nucleic acids, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35. Thus, Applicants are fully entitled to the benefit of these earlier filed applications.

**Rejection under 35 U.S.C. § 101**

The Examiner rejected Claims 1-20 as lacking either a credible, specific and substantial asserted utility or a well-established utility under 35 U.S.C. § 101. According to the Examiner, the specification does not disclose a function for the nucleic acid of SEQ ID NO:93, encoding the polypeptide of SEQ ID NO: 94 in the context of the cell or organism. The PTO rejects each of the asserted utilities, including that PRO1328 is useful in the diagnosis and treatment of cancer. While the PTO acknowledges that the nucleic acid encoding PRO1328 is more highly expressed in normal lung and melanoma tumor compared to lung tumor and normal skin tissue, the Examiner states that a slight increase or decrease in clone copies in tumors is not indicative of a specific or substantial utility for PRO1328. The PTO takes the position that significant further experimentation would be required of the skilled artisan to determine whether PRO1328 is expressed in certain cancers to the extent that antagonists directed against the protein would be expected to have utility in cancer therapy.

Applicants respectfully disagree.

*Utility – Legal Standard*

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added.)

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

*Utility – Evidentiary Standard*

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the PTO must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the PTO has made a proper *prima facie* showing of lack of utility does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

*Substantial Utility - Applicants have established that the Gene Encoding the PRO1328 Polypeptide is Differentially-expressed in Certain Cancers and is Useful as a Diagnostic Tool*

The PTO argues that the invention lacks specific and substantial utility because there is no necessary correlation between a specific disease state and the expression of the PRO1328 polypeptide. According to the PTO, the invention lacks utility, as it is not clear if the expression of the PRO1328 polypeptide is correlated with a specific change in physiology, for example, or with any cancer. The PTO also argues that experiments confirming the specificity and substantial utility of PRO1328 in terms of mRNA and protein expression were not performed. Therefore, the PTO argues that significant further experimentation would be required of the skilled artisan to determine whether PRO1328 is expressed in certain cancers to the extent that antagonists directed against the protein encoded by DNA66658-1584 (PRO1328) would be expected to have utility in cancer therapy.

The claims are directed to isolated nucleic acids, including nucleic acids that encode the polypeptide of SEQ ID NO:94 (PRO1328). The specification, in Example 18, discloses that the nucleic acid encoding PRO1328 (DNA66521-1583) is more highly expressed in normal lung and melanoma tumor compared to lung tumor and normal skin tissue.

The gene expression data in Example 18 was obtained using standard semi-quantitative PCR amplification reactions with cDNA libraries isolated from different human tumor and normal human tissue samples and analyzed by agarose gel electrophoresis so as to obtain a semi-quantitative determination of the level of expression of the PRO polypeptide-encoding nucleic acid in each reaction. Identification of the differential expression of the PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of

the same tissue type rendered the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor, as well as therapeutically, as a target for the treatment of a tumor in a subject possessing such a tumor. Applicants submit herewith as Exhibit 1 the declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. The Declaration was originally submitted in co-pending application Serial No. 10/063,557. This declaration explains the importance of the data shown in Example 18, and how differential gene and protein expression studies are used to differentiate between normal tissue and cancer tissue (see Grimaldi Declaration, Exhibit 1, paragraph 7).

In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues. Mr. Grimaldi explains that:

> The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual. That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. (Paragraph 5).

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal." He explains that, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

*Applicants have Established that the Accepted Understanding in the Art is that there is a Direct Correlation between Comparative mRNA Levels and the Level of Expression of the Encoded Protein in Normal versus Cancerous Tissue*

The Examiner argues that the data presented are not substantial because it is known in the art that increased mRNA levels do not necessarily correlate to an increase in protein production, and do not correlate well. The Examiner relies upon Haynes *et al.* (1998, *Electrophoresis*, 19:1862-1871), asserting that Haynes found that for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold.

As stated above, the standard for utility is not absolute certainty, but rather whether one of skill in the art would be more likely than not to believe the asserted utility. Even if Haynes supported the Examiner's argument, which it does not, one contrary example does not establish that one of skill in the art would find it is more likely than not, that in general, there is no correlation between mRNA level and protein levels. In fact, the working hypothesis among those skilled in the art is that there is a direct correlation between mRNA levels and protein levels.

Haynes does not contradict the utility of the instant claims. Specifically, Haynes does not address the issue of whether levels of mRNA in a tumor cell compared to a normal cell typically correlate to a similar increase/decrease in the amount of the encoded protein in the tumor cell relative to the normal cell. For example, in the case of increased expression of a particular mRNA in a lung tumor cell compared to a non-cancerous lung cell, Haynes does not address whether one would expect to see a corresponding increase in expression of the particular encoded protein in the lung tumor cell compared to the normal lung cell.

Haynes is 1998 a review article dealing with the art of proteome analysis. Haynes studied 80 selected samples, all from one organism, *Saccharomyces cerevisiae.* Haynes considered whether different genes with roughly equivalent mRNA levels would correspond to equivalent protein levels for the different genes. Haynes reported to have "found a general trend but no strong correlation between protein and transcript levels." Thus, it is not even clear that Haynes even supports the Examiner's position, as Haynes did report a general trend, with some exceptions. For some of the studied genes, Haynes reported differences in protein expression between different genes, including some that varied by more than 50-fold. Thus, Haynes showed that for one type of yeast organism, *Saccharomyces cerevisiae*, similar mRNA levels for different genes did not universally result in equivalent protein levels for the different genes. This is

different from whether increased mRNA levels for a single gene in one cell type compared to the same gene in a different cell type, would also correspond to increased protein levels in the one cell type compared to the different cell type. Therefore, Haynes is not inconsistent with or contradictory to the utility of the instant claims.

Applicants further submit that it is generally well-understood in the art that in the majority of cases, gene expression correlates with levels of protein expression. In support of Applicants' position, Applicants submit herewith as Exhibit 2 a second declaration of J. Christopher Grimaldi, also originally submitted in co-pending application Serial No. 10/063,557. As stated in paragraph 5 of this declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed....This same principle applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Scientists regularly rely on the results of gene expression to point the way to differential protein expression in disease and, in this case, cancer. Submitted herewith as Exhibit 3 is the declaration of Dr. Paul Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in

approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceeds this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Additional references support this position. For example, Orntoft et al. (submitted herewith as Exhibit 4) studied transcript levels of 5600 genes in malignant bladder cancers which were linked to a gain/loss of chromosomal material using an array-based method. Orntoft et al. showed that there was a gene dosage effect and teach that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman et al. (submitted herewith as Exhibit 5) showed, using CGH analysis and cDNA microarrays to compare DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there is "evidence of a prominent global influence of copy number changes on gene expression levels" (see page 6244, column 1, last paragraph). Additional supportive teachings are also provided by Pollack et al. (submitted herewith as Exhibit 6) who studied a series of primary human breast tumors and found that "...62% of highly amplified genes show moderately or highly elevated expression, that DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels" (see column 1, abstract). Thus, these articles collectively teach that in general, there is a correlation between gene expression and mRNA expression.

Taken together, despite some teachings in the art of certain genes that do not fit within this paradigm which are exceptions rather than the rule, <u>in the vast majority of cases</u>, the combined teachings in the art, exemplified by Orntoft et al., Hyman et al. and Pollack et al. and the Grimaldi and Polakis declarations, overwhelmingly teach that gene expression influences protein levels. Thus, one of skill in the art would reasonably expect, in this instance, based on

the gene expression data for the PRO1328 gene, that the PRO1328 protein is over-expressed in melanoma tumor and under-expressed in lung tumor as compared to normal tissues of the same type. Thus, Applicants submit that the nucleic acids encoding the PRO1328 protein have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use these molecules.

Applicants submit that they have therefore established two separate bases for utility of the claimed nucleic acids. The first argument is based on the differential expression of the PRO1328 encoding gene in normal lung tissue and melanoma tumor compared to lung tumor and normal skin tissue. The second argument is based on the utility of the PRO1328 polypeptides as diagnostic tools, given that it is well-established in the art that there is a correlation between gene expression and protein expression. As the PTO acknowledges, the utility of the polypeptide confers utility on the encoding gene as well.

*The Claimed Nucleic Acids would have Diagnostic Utility even if there is no Direct Correlation between Gene Expression and Protein Expression*

Even assuming *arguendo* that, there is no direct correlation between gene expression and protein expression for PRO1328, which Applicants submit is not true, a polypeptide encoded by a gene that is differentially expressed in cancer would **still** have a credible, specific and substantial utility.

In paragraph 6 of the Grimaldi Declaration, Exhibit 2, Mr. Grimaldi explains that:

> However, even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy.

This conclusion is echoed in the Declaration of Avi Ashkenazi, Ph.D. (attached as Exhibit 7), an expert in the field of cancer biology. This declaration was previously submitted in connection with co-pending application Serial No. 09/903,925. Applicants submit that simultaneous testing of gene expression and gene product expression enables more accurate tumor classification, even if there is no positive correlation between the two. This leads to better determination of a suitable therapy.

This is further supported by the teachings in the article by Hanna and Mornin (attached as Exhibit 8). The article teaches that the HER-2/neu gene has been shown to be amplified and/or overexpressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the overexpression of the HER-2/neu gene product (by IHC). Even when the protein is not overexpressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Applicants have established that it is the general, accepted understanding in the art that there is a positive correlation between gene expression and protein expression. However, even when this is not the case, a polypeptide encoded by a gene that is differentially expressed in cancer would still have utility, as would the nucleic acid which encodes it. Thus, Applicants have demonstrated another basis for supporting the asserted utility for the claimed nucleic acids.

**Specific Utility**

*The Asserted Substantial Utilities are Specific to the Claimed Nucleic Acids*

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1328 gene in certain types of cancer cells, along with the declarations discussed above, provide a specific utility for the claimed nucleic acids.

As discussed above, there are significant data which show that the gene encoding the PRO1328 polypeptide is more highly expressed in normal lung and melanoma tumor compared to lung tumor and normal skin tissue. These data are strong evidence that the gene encoding the PRO1328 polypeptide is associated with lung and melanoma tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the gene encoding PRO1328 with specific diseases. This is a specific utility – it is not a general utility that would apply to the broad class of nucleic acids.

**Conclusion**

The PTO has asserted two arguments for why there is a lack of a substantial utility: (1) that the data reporting differential expression of the PRO1328 gene in certain cancers is not reliable; and, (2) that because there is no necessary correlation between gene expression and

protein expression, the claimed nucleic acids cannot be used as cancer diagnostic or therapeutic tools. Applicants have addressed each of these arguments in turn.

First, the Applicants provide a declaration stating that the data in Example 18 reporting higher expression of the PRO1328 gene in normal esophagus, stomach, lung, rectum and skin compared to tumor in these same tissue types, are real and significant. This declaration also indicates that given the relative difference in expression levels, the claimed nucleic acids have utility as cancer diagnostic tools.

Next, the Applicants have shown that the reference cited by the PTO to support its conclusion that there is no necessary correlation between the level of gene expression and mRNA or protein expression does not support the PTO's position. Applicants have presented the declarations of two experts in the field along with supporting references which establish that the general, accepted view of those of skill in the art is that there is a direct correlation between mRNA levels and the encoded protein levels. Thus, one of skill in the art would find that it is more likely than not that the PRO1328 protein has utility as a diagnostic tool for cancer, and nucleic acids encoding the polypeptide also have utility as a result.

Applicants have also presented the declarations of two experts in the field, along with supporting references, which establish that even in the anomalous case where there is no positive correlation between gene expression and expression of the encoded protein, the simultaneous monitoring of both is useful for diagnosis and further classification of the cancer.

Applicants have pointed out that the substantial utilities described above are specific to the claimed nucleic acids because the gene encoding PRO1328 is differentially expressed in certain cancer cells compared to the corresponding normal cells. This is not a general utility that would apply to the broad class of nucleic acids.

Thus, given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed nucleic acids as a diagnostic agent. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is <u>not</u> required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed nucleic acids relating to PRO1328 set forth in the specification. In

view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

**Rejection under 35 U.S.C. §112, first paragraph – Enablement**

The PTO rejected Claims 1-20 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. The PTO argues that because the claimed invention is not supported by a substantial, specific and credible utility, the claims are not enabled. Also, the PTO argues that Applicants have not associated the disclosed PRO1328 polypeptide with any type or genus of secreted peptide. Further, relying upon Haynes et al. (*Electrophoresis* 19:1862-1871, 1998), the PTO argues that the results of the experimental assays are not considered substantial because it is known in the art that increased mRNA levels do not necessarily correlate to an increase in protein production, or do not correlate well. The PTO also argues that specification fails to provide evidence to illustrate the relationship between PRO1328 polypeptide and a positive change in cancer cell proliferation. The PTO argues that as many proteins may regulate the PRO1328 peptide, one cannot extrapolate from increased mRNA levels that any protein, such as PRO1328, would be a useful target for treating cancer.

Therefore, the PTO asserts that due to the large quantity of experimentation necessary to determine an activity or property of the disclosed polypeptide of SEQ ID NO: 94 and to screen for activity, the lack of direction/guidance presented in the specification, and the absence of working examples, the complex nature of the invention, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity, and the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite particular biological activities, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

As an initial matter, Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed nucleic acids. Applicants therefore request that the PTO reconsider and withdraw the enablement rejection to the extent that it is based on a lack of utility for the claimed nucleic acids.

Haynes does not contradict the enablement of the instant claims. Specifically, Haynes does not address the issue of whether levels of mRNA in a tumor cell compared to a normal cell typically correlate to a similar increase/decrease in the amount of the encoded protein in the tumor cell relative to the normal cell. For example in the case of increased expression of a particular mRNA in a melanoma cell compared to a non cancerous skin cell, Haynes does not address whether one would expect to see a corresponding increase in expression of the particular encoded protein in the melanoma cell compared to the normal skin cell.

As discussed above, Haynes is 1998 a review article dealing with the art of proteome analysis. Haynes studied 80 selected samples, all from one organism, *Saccharomyces cerevisiae*. Haynes considered whether different genes with roughly equivalent mRNA levels would correspond to equivalent protein levels for the different genes. Haynes reported to have "found a general trend but no strong correlation between protein and transcript levels." Thus, it is not even clear that Haynes even supports the Examiner's position, as Haynes did report a general trend, with some exceptions. For some of the studied genes, Haynes reported differences in protein expression between different genes, including some that varied by more than 50-fold. Thus, Haynes showed that for one type of yeast organism, *Saccharomyces cerevisiae*, similar mRNA levels for different genes did not universally result in equivalent protein levels for the different genes. This is different from whether increased mRNA levels for a single gene in one cell type compared to the same gene in a different cell type, would also correspond to increased protein levels in the one cell type compared to the different cell type. Therefore, Haynes is not inconsistent with or contradictory to the enablement of the instant claims.

Furthermore, Applicants have amended the claims to incorporate the limitation that the claimed nucleic acids with less than 100% identity to SEQ ID NO: 93, or which encode a protein with less than 100% identity to SEQ ID NO: 94, must be more highly expressed in normal lung and melanoma tumor compared to lung tumor and normal skin tissue, or encode a polypeptide that is more highly expressed in normal lung and melanoma tumor compared to lung tumor and normal skin tissue. Applicants assert that techniques used to make variants of polynucleotide or polypeptide sequences are well-known to those of skill in the art (see, e.g., paragraph [0258] of the specification). Thus, the claims as amended contain sufficient structural information to enable the claims.

Applicants also submit that undue experimentation would not be required to use the claimed nucleic acids as diagnostic tools. The level of skill in the art is high, and methods of using nucleic acid sequences as probes are well-known and well-established in the art. One of skill in the art would know how to use the claimed nucleic acids, for example, as hybridization probes for the diagnosis of cancer as outlined in the specification at, for example, paragraph [0336], and Example 18 beginning at paragraph [0529].

Finally, Applicants note that because they have established a utility for the PRO1328 polypeptide, supported by the declarations of two experts in the field, polynucleotides which encode the PRO1328 polypeptide also have utility. This includes degenerate polynucleotide sequences which encode the PRO1328 polypeptide.

In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

**Rejection under 35 U.S.C. §112, first paragraph – Written Description**

The PTO has rejected Claims 1-6 and 8-20 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the invention. According to the PTO, because the specification does not teach functional or structural characteristics of all claimed polynucleotides, the claims fail the written description requirement. The PTO states the factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof, but that the only factor present in the claim is a partial structure in the form of a recitation of percent identity. The PTO concludes that in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

*The Legal Standard for Written Description*

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); see also *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written

description support is a factual issue and is to be determined on a case-by-case basis. See e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

*The Current Invention is Adequately Described*

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains.

The present invention pertains to the field of recombinant DNA/protein technology. It is well established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made. The claims concern nucleic acids having a specified sequence identity with the specified nucleic acid sequence, and as amended, with the functional recitation: "wherein said isolated nucleic acid is more highly expressed in normal lung and melanoma tumor compared to lung tumor and normal skin tissue, or wherein said isolated nucleic acid encodes a polypeptide that is more highly expressed in normal lung and melanoma tumor compared to lung tumor and normal skin tissue." Based on the detailed description of the cloning and expression of variants of PRO1328 in the specification, the description of the gene expression assay, the actual reduction to practice of sequences SEQ ID NOs: 93 and 94, and the functional recitation in the instant claims, Applicants submit that one of skill in the art would know that Applicants possessed the invention as claimed in the instant claims. Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

**Rejection under 35 U.S.C. §112, first paragraph – Deposit Rules**

Claims 1-6, 8-10 and 11-13 are rejected as not complying with the enablement requirement, since the deposit requirements were not met. The Examiner requests a Declaration by Applicants or assignees, or a statement by an attorney of record, that the deposit has been

made under the provisions of the Budapest Treaty and that the nucleic acid molecules will be irrevocably and without restriction or condition released to the public upon the issuance of a patent to satisfy the deposit requirement. Although paragraph [446] of the specification states that permanent and unrestricted availability of the deposits will be provided upon issuance of the pertinent U.S. Patent or laying open to the public of any U.S. or foreign patent application, whichever comes first, to facilitate allowance of the present application, Applicants provide the requested Declaration herewith.

**Rejections under 35 U.S.C. § 112, second paragraph – Indefiniteness**

The PTO has rejected Claims 1-6, 9, 10 and 14 under 35 U.S.C. § 112, second paragraph, as being indefinite. The PTO objects to the phrase "the extracellular domain" as the polypeptides encoded by the claimed nucleotides are implied and stated to be secreted proteins. Thus, "the extracellular domain" is not recognized in secreted proteins since they are entirely extracellular.

Figure 94 discloses that the protein includes transmembrane domains at amino acids 32-51, 119-138, 152-169 and 216-235. The claims have therefore been amended to recite the specific regions comprising the extracellular domains, namely, amino acids 20-31, 139-151, and 236-257.

The PTO also rejected Claim 15 as being indefinite because of the phrase "stringent conditions." The PTO indicated that the rejection can be overcome by supplying the specific conditions, which are considered as being "stringent." Claim 15 has been cancelled and Claim 14 has been amended to recite specific "stringent" conditions.

Applicants therefore request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

**Rejection under 35 U.S.C. §102(b) – Anticipation**

The PTO rejects Claims 16 as anticipated under 35 U.S.C. § 102(b) by Laird, G. (Accession No. AL445222, submitted April 24, 2001). The PTO states that Laird disclose a polynucleotide sequence that has several segments at least 10 nucleotides in length that are identical to the corresponding segments of the claimed polynucleotides. Applicants respectfully traverse.

As discussed above, Applicants claim priority to, among other applications, PCT Application PCT/US00/23328, filed on August 24, 2000. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the

claimed nucleic acids, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35. Laird with its submission date in 2001, is not prior art under 102.

Thus, Applicants respectfully submit that the cited reference is not available as prior art, and request that the rejection under 35 USC §102 be withdrawn.

**Conclusion**

The present application is believed to be in condition for allowance, and action to that effect is respectfully solicited. Applicants invite the Examiner to call the undersigned if any issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: October 27, 2004

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